REMARKS

Claim Status

Claims 1, 6-7, 20-21, 23-26 and 35-36 are pending after entry of this paper. Claims 1, 6-7, 20-21, 23-26 and 35-36 have been rejected. Claims 2-5, 8-19, 22 and 27-34 have been previously cancelled without prejudice. Claims 23 and 24 have been cancelled without prejudice. Applicants reserve the right to pursue cancelled claims in a divisional or a continuing application.

Claims 1 and 35 have been amended to add "that does not replicate in adult normal cells, that induces a viral gene expression and a viral replication specifically in a proliferating cells that express calponin, and that is capable of suppressing its replication at a desired timing by using the thymidine kinase gene" in the preamble. Support may be found throughout the instant specification and the claims as originally filed, for example, pages 9-12 of the Exhibit B.

Claims 1, 6 and 35 have been amended to replace "a region containing promoter" with "a promoter region." Claims 1 and 35 have been further amended to identify the human calponin gene by SEQ ID NO.:3. Claims 1 and 35 have been amended to replace "index" with a "marker."

Claim 1 has been amended to clarify that the vector is TK+. In other words, the tymidine kinase gene is already present within the vector DNA and no further insertion is required. Support may be found in paragraph bridging pages 11 and 12 of Exhibit B.

Claim 35 has been amended to clarify the positive steps of the method for producing a cell-specific HSV vector.

No new matter is added by the instant amendment. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Objection to the Specification

The Examiner objects to the specification and requested a substitute specification in idiomatic English with corrected headings. To comply with Examiner's request, applicants respectfully submit herewith a substitute specification in accordance with 37 C.F.R. §1.121(b)(3). No new matter has been added to the specification by this amendment. Applicants believe the specification as amended is in proper idiomatic English with correct heading, and respectfully request withdrawal of the objections to the specification.

Response to Rejections under 35 U.S.C. §103(a)

Claims 1, 6, 7, 20, 21, 25, 35, and 36 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al. (U.S. Patent No. 5,728,379) in view of Chung, et al. (*J. Virol.* 73:7556-7564, 1999), Yamamura, et al. (*Cancer Research* 61:3969-3977, 2001), Wagstaff, et al. (*Gene Therapy* 5: 1566-1570, 1998) and Foster (*J. Virol. Methods* 75: 151-160, 1998). Applicants respectfully disagree and assert that contrary to the Examiner's contention, the claimed invention is not made obvious by the combination of Martuza, Chung, Yamamura, Wagstaff, and Foster.

According to the Examiner, Martuza allegedly teaches an HSV vector with a cell-specific promoter, ICP4 gene downstream to such promoter, lacZ upstream to the promoter, and tissue-specific enhancers upstream to the tissue-specific promoter (Office Action – page 3). Furthermore, the Examiner contends that Martuza teaches that the DNA fragment could be

inserted anywhere other than the *tk* (thymidine kinase) locus, which would retain the sensitivity to ganciclovir (Office Action – page 3). However, applicants respectfully assert that the plurality of vectors with different features suggested by Martuza and relied by the Examiner comprise features that are contradictory to each other and a vector of interest cannot be produced through a mere combination of the elements of each vector.

> [I]n determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). (emphasis added; MPEP 2141)

The Examiner indicates that "Martuza et al. teach that ribonucleotide reductase gene disruption is essential for therapeutic vectors, wherein the ribonucleotide reductase-disrupted vectors are less likely to replicate in normal cells (column 22, line 1-3 and 24-40, column 25, lines 57-62)" (Office Action, page 4, lines 14-18). Such description, however, concerns TK- (minus) vectors, and the reason for this is shown as follows: "Because TK-HSV-1 mutants known in the art are resistant to these anti-viral agent, such mutant could be difficult to eliminate in the event of systemic infection or encephalitis." (column 22, lines 27-29). In fact, since Martuza teaches that RR disruption is essential only for TK- vectors and suggest nothing about the importance of RR disruption in TK+ (plus) vectors, the teaching of Martuza would not motivate one skilled in the art to select ribonucleotide reductase gene as a region for the insertion of a DNA fragment when using a TK+ vector. However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims 1 and 35 to add "HSV vector that comprises an endogenous thymidine kinase

gene . . ." Therefore, the instant invention would not have been obvious based at least on the teachings of Martuza et al.

The Examiner acknowledges that Martuza does not teach the process of inserting the DNA fragment into the ribunucleotide reductase locus, which according to the Examiner is allegedly made obvious by Chung (Office Action, pages 4-5). Specifically, the Examiner suggests that the vector of the instant invention would have been obvious to a skilled artisan by combining the teachings of Martuza and Chung, where Martuza teaches that a DNA fragment comprising ICP4 operably linked to a tissue specific promoter can be inserted by homologous recombination in any location of the HSV genome, and Chung teaches insertion of a DNA comprising a tissue specific promoter operably linked to a gene essential for HSV virulence into the rebonucleotide reductase gene locus.

Applicants respectfully assert that even if for an argument sake it would be possible, as the Examiner indicated, to insert a DNA comprising the tissue specific promoter of Martuza into the ribonucleotide reductase locus of the mutant HSV vector G92A as disclosed in Fig. 1 in Chung, when such vectors are produced, it is impossible to isolate the vector of interest due to the absence of markers for distinguishing vectors that underwent recombination and those that did not. Since the backbone vector which Chung used for recombination was a mutant HSV vector in which *LacZ* had been inserted into the ribonucleotide reductase locus, it was possible to conduct screening to see whether the DNA was inserted or not by using deletion of the *LacZ* expression as a marker. On the contrary, because the vector taught in Martuza has no insertion of a marker gene such as *LacZ* at the ribonucleotide reductase locus, vectors cannot be produced in the same manner as Chung and would require additional undue experimentation.

When the DNA fragment of Martuza is introduced into the ribonucleotide reductase locus while the *tk* gene is left intact, it is impossible to select recombinants based on the sensitivity to ganciclovir. Selection of recombinants based on the sensitivity to ganciclovir is only enabled when the DNA fragment is inserted into the *tk* locus. Further, when "a DNA fragment comprising a tissue-specific promoter, the ICP4 gene downstream to the tissue-specific promoter, and *lacZ* upstream to the tissue-specific promoter" taught in Martuza is introduced into "a vector wherein the ribonucleotide reductase locus is disrupted by *lacZ* insertion" taught by Chung, LacZ will be present in both of the vectors that underwent recombination and that did not. Therefore, it is impossible to isolate only those vectors that underwent recombination. In view of the above, the instant invention would not have been obvious from the teachings of Martuza and Chung.

Moreover, applicants respectfully assert that in order to produce a recombinant vector, it is necessary not only to insert a DNA fragment into a vector but subsequently to isolate the recombinants of interest in which appropriate insertion has occurred from negative vectors (those vectors in which no insertion has occurred, or only part of the DNA fragment has been inserted). The Examiner states that "Chung et al. teach recombination at the RR locus and the nature of the DNA fragment to be inserted is irrelevant" (Office Action, page 12, lines 22-23). On the contrary, the nature of the DNA fragment to be inserted largely affect the isolation step of vectors after insertion. Unless an appropriately designed DNA fragment is used, it is not possible to select recombinants into which the DNA fragments are inserted and the recombinants of interest cannot be established. Therefore, the assertion that "any gene can be inserted by following Chung's teachings" (Office Action, page 13, lines 11-12) is inaccurate. This notion is supported by the fact that the Martuza's group was only able to produce the HSV vector

comprising the ICP4 gene which is linked to a cell-specific promoter inserted in the ribonucleotide reductase locus for the first time in 2006, well after the date of Martuza and Chung provided the alleged teachings to produce the vector of the instant invention..

Furthermore, the assertion that "Chung et al. teach insertion of a DNA comprising a tissue specific promoter operably linked to a gene essential for HSV virulence into the ribonucleotide reductase locus (p. 7558, Fig. 1, p. 7557, column 1, second paragraph and column 2, Results)" (Office Action; pg. 5, lns 2-5) is inaccurate. The vector of Chung is not a tissue specific promoter but a cell cycle regulated promoter. Indeed, Chung expressly states in the Abstract, line 6, and page 7562, right column, 4th paragraph that B-myb promoter is a promoter that is regulated in a cell cycle-specific manner. In addition, the experimental results of Chung (page 7559, 2nd paragraph) demonstrate that their vector is a cell cycle specific vector and not a cell type specific vector.

Finally, in response to applicants previous arguments, the Examiner contends that "making a construct [of the instant invention] was routine in the prior art, as demonstrated by Chung." (Office Action; pg. 12; lns. 9-12). Applicants respectfully disagree. The construct of Chung was produced by the steps of transfecting Vero cells with a linearized gene fragment and the vector, harvesting virus progeny when cytopathic effect by the γ34.5 gene expression were evident, and confirming deletion of the LacZ gene by Southern blot analysis and agarose overlay assay, thus isolating the recombinant vector of the interest, as described in page 7557, left column, MATERIALS AND METHODS, 2nd paragraph, lines 16-20. However, a screening method using cytopathic effect and agarose overlay assay as that of Chung cannot be applied to production (selecting) of the vector of the present invention. Therefore, making a construct of the instant invention can not be considered routine as suggested by the Examiner.

With respect to the teaching of the calponin promoter and the 4F2 enhancer of the instant invention, the Examiner acknowledges that Martuza and Chung do not teach the full length calponin promoter or the 4F2 enhancer, but they are allegedly taught by Yamamura. Specifically, Yamamura teaches a calponin promoter which promotes expression of the ICP4 gene, and the 4F2 enhancer which is integrated to the upstream of the calponin promoter and which enhances expression of ICP4. However, applicants respectfully assert that it is extremely difficult to produce a recombinant where the Yamamura's sequence consisting of the 4F2 enhancer, calponin promoter, and ICP4 is introduced into a region other than the TK locus in the HSV vector. It became possible to produce the vector of the instant invention at last by adding another marker sequence (adding EGFP to the downstream of IRES) to the introductory sequence of Yamamura et al. so as to enabling a reliable screening of recombinants to a region other than the TK locus in the HSV vector.

While Wagstaff show that the use of an IRES enables the translation of two reporter genes from a single mRNA transcript derived by a single promoter (Abstract, right column, lines 3-8), in the instant invention, two marker genes are controlled by different promoters. LacZ is placed upstream to the calponin promoter and EGFP is placed downstream to the ICP4, which is under the control of the calponin promoter. Essentially, the two markers are translated from different mRNAs, not from the same mRNA taught by Wagstaff. Hence, the HSV Vector prepared following the teachings of Martuza, Chung, Yamamura, and Wagstaff would not function/operate with its intended purpose and, therefore, can not be used as the basis for the *prima facie* obviousness rejection.

Therefore, in view of the arguments presented above, applicants assert that none of the references, either alone or in combination, discloses all of the elements to produce the claimed HSV vector. One skilled in the art would not look to Chung or Wagstaff to overcome the deficiencies of Martuza, Yamamura, and Foster. Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) of the claims 1, 6, 7, 20, 21, 25, 35, and 36 are respectfully requested.

Claims 1, 6, 7, 20, 21, 25, 26, 35, and 36 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al., in view of Chung, et al., Yamamura, et al., Wagstaff, et al., Foster, and Miyatake, et al., (*Stroke*, 30:2431-2439, 1999). Specifically, claims 1, 6, 7, 20, 21, 25, 26, 35, and 36 stand rejected over Martuza, Chung, Yamamura, Wagstaff, and Foster, while claim 26 is allegedly made further obvious in view of Miyatake. Applicants respectfully disagree.

Applicants respectfully assert that Martuza in view of Chung, Yamamura, Wagstaff, and Foster do not teach each and every element of the claimed invention. Moreover, the addition of Miyatake does not remedy the deficiencies of the combination of Martuza, Chung, Yamamura, Wagstaff, and Foster. Specifically, applicants respectfully assert that Miyatake does not cure the deficiencies of Martuza noted in the previous subsection even in combination with Chung, Yamamura, Wagstaff, and Foster.

> [T]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S., 82 USPQ2d 1385, 1396 (2007) (MPEP 2141)

Applicants respectfully assert that the results would not be predictable to one of ordinary skill in the art without undue experimentation because Miyatake teaches a self-replicable HSV vector that is not cell-specific and substantially different from the cell-specific vector of the instant invention as discussed above. In particular, the Miyatake HSV vector is recombinant with *LacZ* gene within the RR locus. While RR (ICP6) gene is specific for proliferating and nonproliferating cells (dividing cell-specific) as noted by Miyatake because the RR enzyme is critical in the *de novo* synthesis of DNA precursors, the HSV vector designed by Miyatake is not tissue specific, e.g., vascular smooth muscle cells, unless the vector is directly injected into the area where the target cells are. Therefore, a skilled artisan would have to perform a substantial amount of experimentation to properly and successfully combine the teachings of Martuza, Chung, Yamamura, Wagstaff, Foster and Miyatake in order to arrive at the claimed invention. In order to satisfy the rejection on the grounds of *prima facie* obviousness, the combination must be more than mere possibility, a skilled artisan while applying a routine experimental procedures should be able to combine the references suggested by the Examiner without any undue experimentation with anticipation of success. Thus, applicants contend that the proposed combination of references "would [not] have been predictable to one of ordinary skill in the art" (MPEP 2141) For at least these reasons, reconsideration and withdrawal of the rejections of the claims 1, 6, 7, 20, 21, 25, 26, 35, and 36 are respectfully requested.

Claims 1, 6, 7, 20, 21, 23-25, 35, and 36 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al., in view of Chung, et al., Yamamura, et al., Wagstaff, et al., Foster, and further in view of Tjuvajev, et al. (*Cancer Research*, 58:4333-4341, 1998). According to the Examiner, Martuza, Chung, Yamamura, Wagstaff, and Foster teach the

claimed invention as disclosed in claims 1, 6, 7, 20, 21, 25, 35, and 36 except that they do not teach detecting the *in vivo* distribution of the vector by determining *tk* activity using PET and FIAU labeled with ^{124}I of instant claims 23 and 24, which is allegedly made obvious by the disclosure of Tjuvajev. Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have cancelled claims 23 and 24. Therefore, the instant rejection is moot. Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) of the claims 1, 6, 7, 20, 21, 23-25, 35, and 36 are respectfully requested.

Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claims 1 and 35 from which all of the dependent claims 6, 7, 20-21, 23-26, and 36 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

CONCLUSION

Based on the foregoing amendments and remarks, the applicants respectfully request reconsideration and withdrawal of the pending rejections and allowance of this application. The applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of

this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-4827**, Order No. 1004331.019US.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-4827**, Order No. 1004331.019US.

Respectfully submitted,
Locke Lord Bissell & Liddell LLP

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By: /Serge Ilin-Schneider/
Serge Ilin-Schneider, Ph.D.
Registration No. 61,584

Correspondence Address:
Locke Lord Bissell & Liddell LLP
3 World Financial Center
New York, NY 10281-2101
(212) 415-8600 Telephone
(212) 303-2754 Facsimile